

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
9 June 2005 (09.06.2005)

PCT

(10) International Publication Number
WO 2005/051882 A1

(51) International Patent Classification⁷: **C07C 51/36,**
59/64

(21) International Application Number:
PCT/JP2004/017998

(22) International Filing Date:
26 November 2004 (26.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2003-398201 27 November 2003 (27.11.2003) JP

(71) Applicant (for all designated States except US):
TAKASAGO INTERNATIONAL CORPORATION
[JP/JP]; 37-1, Kamata 5-chome, Ohta-ku, Tokyo 1448721
(JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **YOKOZAWA,**

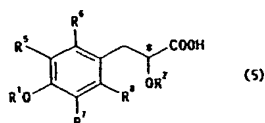
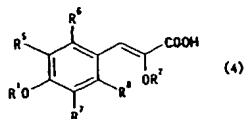
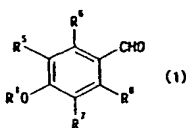
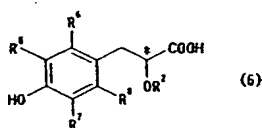
Tohru [JP/JP]; c/o TAKASAGO INTERNATIONAL CORPORATION, Central Research Laboratory, 4-11, Nishiyawata 1-chome, Hiratsuka-shi, Kanagawa 2540073 (JP). **SHIMIZU, Hideo** [JP/JP]; c/o TAKASAGO INTERNATIONAL CORPORATION, Central Research Laboratory, 4-11, Nishiyawata 1-chome, Hiratsuka-shi, Kanagawa 2540073 (JP). **FUJIWARA, Takahiro** [JP/JP]; c/o TAKASAGO INTERNATIONAL CORPORATION, Central Research Laboratory, 4-11, Nishiyawata 1-chome, Hiratsuka-shi, Kanagawa 2540073 (JP). **INO, Yasunori** [JP/JP]; c/o TAKASAGO INTERNATIONAL CORPORATION, Central Research Laboratory, 4-11, Nishiyawata 1-chome, Hiratsuka-shi, Kanagawa 2540073 (JP).

(74) Agent: **IWATANI, Ryo**; Sakurabashi Chiyoda Bldg. 5F, 1-27, Dojima 2-chome, Kita-ku, Osaka-shi, Osaka 5300003 (JP).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,

[Continued on next page]

(54) Title: PROCESS FOR PRODUCING OPTICALLY ACTIVE 3-(4-HYDROXYPHENYL)PROPIONIC ACIDS



(57) Abstract: The present invention relates to a process for producing an optically active 3-(4-hydroxyphenyl)propionic acid useful as intermediates for medicines, through short steps in good yield and with high optical purity. More specifically, the present invention relates to a process for producing an optically active 3-(4-hydroxyphenyl)propionic acid of the formula (6): wherein R² is an alkyl group; R⁵ to R⁸ are each independently a hydrogen atom or a substituent; and the symbol * is an chiral carbon atom, or a salt thereof, which comprises reacting a benzaldehyde of the formula (1): wherein R¹ is a protective group; and R⁵ to R⁸ are each the same as defined above, with a glycolic acid derivative of the formula (2): wherein R³ is a hydrocarbon group; and R² is the same as defined above, hydrolyzing the resulting product to give a cinnamic acid of the formula (4): wherein R¹, R² and R⁵ to R⁸ are each the same as defined above, or a salt thereof, and subjecting the resulting cinnamic acid (4) or a salt thereof to asymmetric hydrogenation to give an optically active phenylpropionic acid of the formula (5): wherein all the symbols are each the same as defined above, or a salt thereof, followed by deprotection.



CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW. ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.